J Headache Pain (2000) 1:179–186

ORIGINAL ARTICLE

Seref Demirkaya
Babur Dora
Mehmet Akif Topcuoglu
U. Hıdır Ulas
Okay Vural

A comparative study of magnesium, flunarizine and amitriptyline in the prophylaxis of migraine

Received: 28 August 2000
Accepted in revised form: 10 January 2001

This study was presented on 5 September 1999 at the 9th European Neurologic Society Meeting, Milan, Italy.

S. Demirkaya (✉) • B. Dora
M.A. Topcuoglu • U.H. Ulas • O. Vural
Neurology Department,
Gülhane Military Medical Academy,
GATA Nöroloji Klinigi 06018, Etlik,
Ankara, Turkey
e-mail: seref@gata.edu.tr
Tel.: +90-3044479
Fax: +90-3044475

Abstract Circumstantial evidence points to the possible role of magnesium (Mg^{+2}) deficiency in the pathogenesis of migraine and has raised questions about the clinical utility of magnesium as a therapeutic regimen in migraine. This was a prospective, randomized, double-blind, placebo-controlled trial comparing the efficacy and tolerability of 1830 mg magnesium citrate (23 patients), 10 mg flunarizine (22 patients) and 10 mg amitriptyline (20 patients) with placebo (22 patients) in the prophylaxis of migraine diagnosed according to the criteria of the International Headache Society. Patients were evaluated for attack frequency, severity and drug side effects monthly for 3 months. Magnesium, flunarizine and amitriptyline were all superior to placebo ($p<0.001$) in reducing both attack frequency and severity after the first month. There was no significant difference between the 3 active drugs in reduction of attack frequency and severity. No serious side effects were observed and the frequencies of side effects were not significantly different in all treatment groups. Our results show that oral magnesium is an effective and well tolerated drug in the prophylaxis of migraine and compares well to established drugs like flunarizine and amitriptyline both in effectiveness and occurence of side effects. Magnesium may be an alternative drug in migraine prophylaxis, but more and larger comparative trials are needed to confirm these results.

Key words Migraine prophylaxis • Amitriptyline • Flunarizine • Magnesium

Introduction

Migraine is a common, chronic disorder often incapacitating its sufferers; approximately 15% of migraineurs suffer from more than two attacks per month and require prophylactic medication [1]. Many drugs of different categories have been used in migraine prophylaxis so far. As they have to be used for a long time, their efficiency is frequently shadowed by their side effects, sometimes resulting in discontinuance of the drug [2–7]. The most commonly used drugs for migraine prophylaxis are beta-blockers, tricyclic antidepressants, especially amitriptyline, and calcium channel blockers, especially flunarizine [5–15].

Circumstantial evidence points to the possible role of magnesium (Mg^{+2}) deficiency in the pathogenesis of migraine and has raised questions about the clinical utility of magnesium as a therapeutic regimen in migraine [16–18]. Studies using magnesium for the prophylactic treatment of migraine have gained interest lately [19–22], most of them showing a good prophylactic effect of magne-

sium versus placebo and a good tolerability of the drug [19, 21, 22]. Although there have been placebo-controlled trials investigating magnesium in migraine prophylaxis, no study has compared magnesium to other drugs commonly used in migraine prophylaxis. We compared the efficacy and tolerability of magnesium with that of flunarizine, amitriptyline and placebo in the prophylaxis of migraine.

Materials and methods

This was a prospective, randomized, double-blind, and placebo-controlled study. Ninety-two patients (68 women, 24 men) suffering from migraine with or without aura and diagnosed according to the criteria of the International Headache Society (IHS) [23] were randomized. Their ages ranged from 20 to 54 years (mean, 31.2 years). The investigators were neurologists with experience in the diagnosis and treatment of headache. The study was conducted in accordance with the Declaration of Helsinki.

All patients were informed of, consented to and underwent a complete physical and neurological assessment. Hematological and biochemical parameters, and electrocardiograms were obtained before entering the trial.

Our inclusion criteria were a normal systemic and neurological examination, 3 or more migraine attacks per month, not having taken any prophylactic medication for the last 4 months and no regular usage of any medication except for oral contraceptives. Our exclusion criteria were suffering from heart, liver or renal disease, a blood pressure over 180/95 mm Hg, pregnancy or lactation, usage of alcohol and having more than 10 attacks of migraine per month. Patients matching our criteria were followed for one month, and were told to keep a diary of the number and intensity of their migraine attacks during this month and not to use any analgesic or antimigraine medication except for oral ergotamin-caffeine combination during the attacks. All patients were strictly advised and did not use ergotamine preparations more often than twice a week and in a greater dose than 4 mg/day when needed. At the end of the one-month period, patients were reassessed, and those with marked differences in attack frequency, duration and intensity compared to the last 4 months as well as those whom we thought to be unable to comply were excluded.

Patients entering the trial were divided into 4 groups. Initially there were 100 patients, 25 in each group, but 1 patient in the magnesium group, 2 in the flunarizine group, 3 receiving amitriptyline and 2 on placebo failed to show up after initiation of the study. These patients were excluded and all analyses were done on the remaining 92 patients. The first group, comprising 24 patients, was given 1830 mg magnesium citrate per day in 3 equal doses. The second group, comprising 23 patients, was given 10 mg flunarizine per day once every evening. Twenty-two patients in the third group received 10 mg amitriptyline per day once every night. The last group, our control group comprising 23 patients, received placebo three times a day. All patients were followed monthly for 3 months, and attack frequency, intensity and drug side effects were noted. Evaluations were done by a neurologist blind to the treatment given. Attack frequency was counted from the last follow-up. Pain intensity was graded in four categories: 0, no pain; 1, mild pain not interfering with daily activities; 2, medium pain, the pain affects daily activities but does not hinder them; and 3, severe pain, hindering almost all daily activities.

All values were displayed as mean ± SD. Categorical variables were compared by chi-square test. One-way ANOVA with post-hoc Tukey's b test and ANOVA for repeated measures were used to compare the numeric variables among drug groups and within each group, respectively. For correlations, two-tailed Pearson's test was used. Significance level was set at 0.05. All analyses were performed using SPSS 8.0 software program.

Results

During the study there were 5 dropouts from the 92 patients participating. In the placebo group, one patient discontinued the medication because of ineffectiveness at the end of the first month. The other four patients retreated from the study due to drug side effects (severe diarrhea in one taking magnesium, daytime sedation in one taking flunarizine and remarkable drowsiness in two taking amitriptyline). The remaining 87 patients completing the study were taken into the analysis. Their ages ranged from 20 to 54 years (mean, 32.6±7.1 years) and 65 were women and 22 were men. Migraine with aura was diagnosed in 32 (36.7%) patients; 65 (74.7%) of enrolled patients had severe attacks, whereas 22 (25.3%) had only moderate attacks. Forty-two patients also complained of episodic attacks of tension-type headache, but the frequency of these attacks was not more than 5 per month and no patient had more than 15 days with headache per month. The patients were advised not to take any medication for these attacks as well. All patients were strictly advised and did not use ergotamine preparations more often than twice a week and in a greater dose than 4 mg/day when needed. None of them used ergotamine preparations for all of their migraine attacks and none of them fulfilled the IHS criteria for ergotamin-induced headache. The patient with the highest attack frequency, complaining of 8 migraine attacks per month, only used ergotamine in 5 of them; two of the three attacks not necessitating medication were at the end of the follow-up month. This knowledge was helpful in excluding the possibility of headaches due to ergotamine abuse. The demographic characteristics and migraine history details of all patients were similar across the treatment groups as were the accompanying symptoms observed during migraine attacks (Table 1).

The comparative effects of the study drugs and placebo on the monthly frequency of migraine attacks are given in Table 2. Treatment with any of the drugs significantly reduced the number of attacks compared to placebo after the first month. Moreover, a significant reduction in attack frequency appeared with each active drug regimen at the end

Table 1 Demographics and migraine characteristics of the 87 patients completing the study

	Magnesium (n = 23)	Flunarizine (n = 22)	Amitriptyline (n = 20)	Placebo (n = 22)
Mean age, years	32.6±6.4	35.1±8.0	30.4±7.0	32.4±6.7
Women, n	17	17	15	16
Aura, no. of patients	9	5	10	8
Mean attack frequency per month	4.22±1.31	4.14±1.25	4.30±1.26	4.32±1.13
Mean attack severity	2.74±0.45	2.86±0.35	2.65±0.49	2.73±0.46
Attack, no. of patients				
Severe	17	19	13	16
Moderate	6	3	7	6

Table 2 Comparative efficacy of medications

	Magnesium (n = 23)	Flunarizine (n = 22)	Amitriptyline (n = 20)	Placebo (n = 22)
Frequency				
Baseline	4.22±1.31	4.14±1.25	4.30±1.26	4.32±1.13
Month 1	3.52±1.38	3.55±1.26	3.70±1.13	4.05±1.05
Month 2	2.22±1.91	2.59±1.01	2.70±0.92	4.00±1.27*
Month 3	1.52±1.34	1.73±1.42	1.90±0.97	3.81±1.14*
Severity				
Baseline	2.74±0.45	2.86±0.35	2.65±0.49	2.73±0.46
Month 1	2.39±0.84	2.55±0.51	2.61±0.49	2.59±0.50
Month 2	1.65±0.98	1.55±0.67	1.70±0.57	2.50±0.51*
Month 3	1.13±0.81	1.05±0.65	1.35±0.74	2.55±0.59*

* Higher with placebo than with other medications, one-way ANOVA with post-hoc multiple comparisons by Tukey's b method ($p<0.001$)

of the first month when comparisons were performed with their pre-treatment values. But when the effects of the 3 active drugs, amitriptyline, flunarizine and magnesium, were compared with each other there was no significant difference between them in reducing attack frequency. The preventive effect of magnesium tended to appear earlier than the other drugs (Figs. 1, 2).

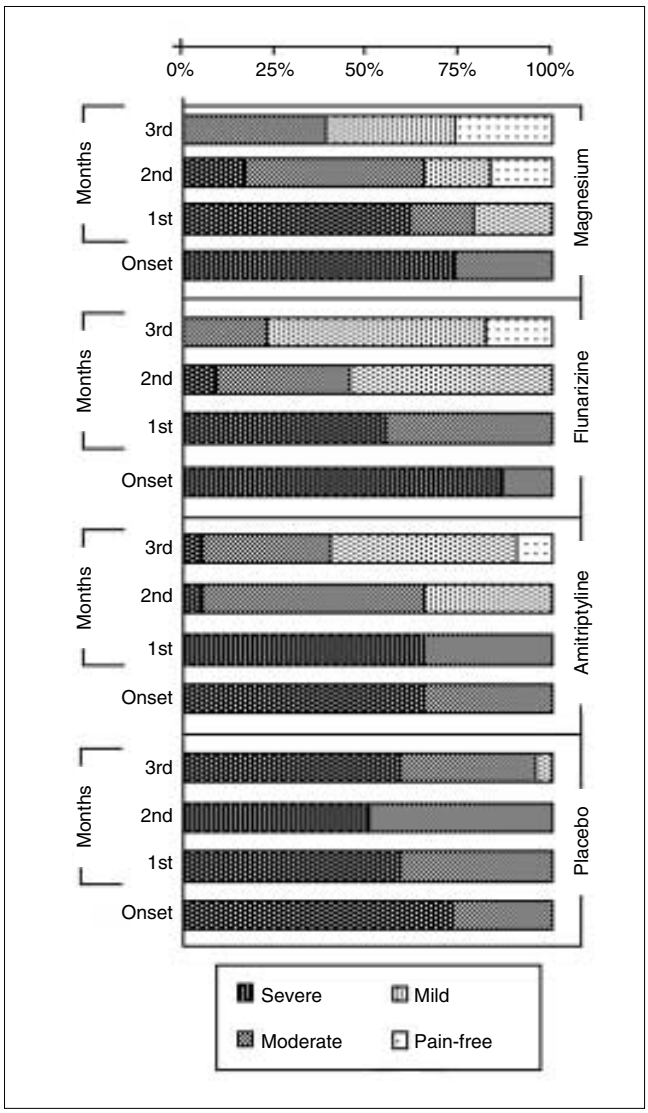
Severity of migraine attacks was also significantly reduced in comparison to placebo after the first month. By intrasubject analysis, both magnesium and flunarizine provided a significant benefit by reducing attack severity at this time but this was not the fact for amitriptyline. After the end of the second month, neither drug was superior to the other in this respect (Fig. 3). The changes in attack severity are displayed in Fig. 1.

Attack frequency and attack severity showed no significant correlation. Attack severity was diminished in all patients using flunarizine and in 95%, 91.3% and 37.3% of patients using magnesium, amitriptyline and placebo, respectively. The efficacy of the study drugs on severe attacks is shown in Fig. 2. All drugs were found to be equally preventive on severe attacks. Effects on moderate attacks were not separately analyzed from the sample size.

Eighteen patients became painfree at the end of 3 months: 7 (29.1%) in the magnesium group, 6 (26%) taking flunarizine, 4 (18.1%) taking amitriptyline and 1 (4.3%) in the placebo group. There was no significant difference among the painfree rates of the treatment drugs.

No serious side effects were observed in the patients during the study. Drugs were discontinued in four patients because of side effects during the study. Frequency of side effects in patients completing the study were 47.8%, 72.7%, 70% and 41% in those using magnesium, flunarizine, amitriptyline and placebo, respectively. Reported side effects with magnesium, sometimes in combination, were stool softening (n = 11, one of whom reported severe diarrhea), appetite gain (n = 1), drowsiness (n = 2), asthenia (n = 3), nausea and/or dyspepsia (n = 4) and dry mouth (n = 5).

Fig. 1 Changes in attack severity



During flunarizine therapy, side effects were appetite gain (n = 14), depression (n = 1), drowsiness (n = 3), asthenia (n = 6), dyspepsia (n = 6), dry mouth (n = 4) and constipation (n = 1). The adverse events reported by patients taking amitriptyline were appetite gain (n = 2), drowsiness (n = 8), asthenia (n = 5), dyspepsia (n = 2), dry mouth (n = 13), and constipation (n = 7). Two patients in the placebo group complained of appetite gain. The other side effects in placebo patients were drowsiness (n = 1), asthenia (n = 4), dyspepsia (n = 6), dry mouth (n = 6) and constipation (n = 2).

Fig. 2 Efficacy of 3 drugs and placebo on severe attacks

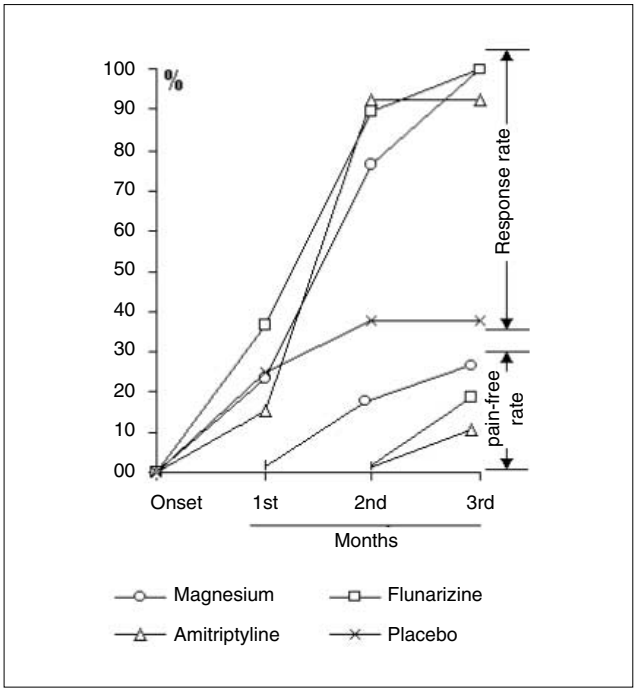
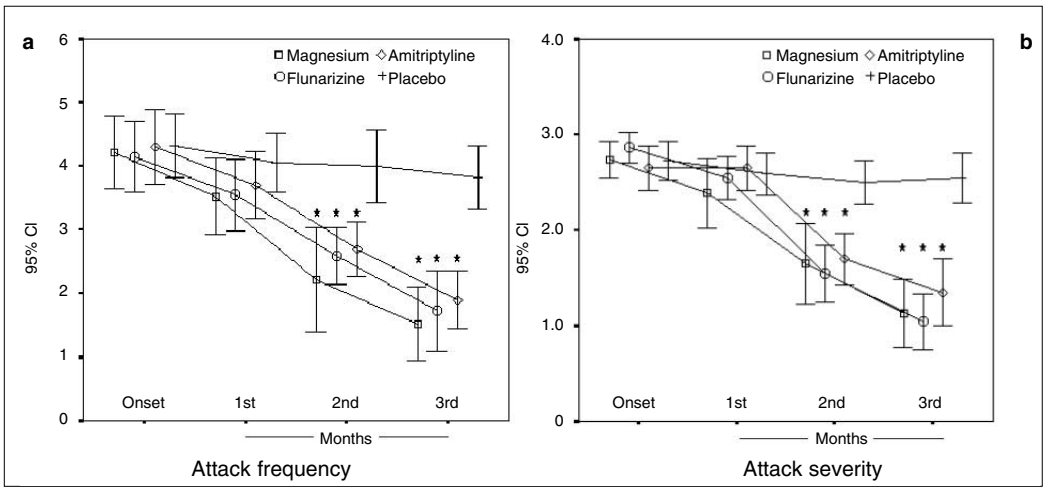


Fig. 3a,b Effect of medications on attack frequency and severity. *p<0.05



Discussion

Magnesium deficiency has been shown to play a possible role in the pathogenesis of migraine during the past two decades [16–18]. This has led to trials questioning the utility of magnesium as a therapeutic choice in the prophylaxis of migraine [19–21, 22]. In most of these trials oral magnesium therapy has been shown to reduce attack frequency significantly when compared to placebo [19, 21, 22]. But none of them has compared magnesium to any other drug commonly used in migraine prophylaxis. In this study we compared magnesium citrate in a higher dose than used in other trials to flunarizine and amitriptyline. Although these two drugs are not first choice drugs for migraine prophylaxis, they are commonly used and have been shown to be effective [5–7, 9–11, 13, 15].

We showed that 1830 mg oral magnesium citrate reduced mean attack frequency by 64% compared to placebo (12%) after 3 months of treatment. This is somewhat higher than the results of Peikert et al. who found that magnesium reduced the mean attack frequency by 41.6% [21] and Taubert who achieved a reduction of 33% [19], both using a magnesium dosage of 600 mg/day. Our higher success rates may be the result of the higher dose of magnesium we used. Peikert et al. [21] reported that magnesium was even significantly superior to placebo at the end of the second month, which was also the fact in our study. Pfaffenrath et al. [20], on the contrary, found no benefit of magnesium compared to placebo during an interim analysis and decided to discontinue their trial.

Mean attack severity was reduced by 59% with magnesium compared to 7% with placebo in our study, leading us to the conclusion that magnesium was also superior to placebo in reducing attack severity. Similar results have been reported in other studies. Peikert et al. [21] also reported that magnesium was more effective in reducing attack severity than placebo (34% vs. 20%) but their results did not reach statistical significance. This was also the fact in the study of Taubert where there was no significant difference between magnesium (44%) and placebo (24%) in reducing attack severity [19], though the results were in favor of magnesium. In another study, 300 mg oral magnesium pyrrolidone carboxylic acid reduced both attack frequency and intensity in the patients with menstrual migraine [22].

We found that all three drug regiments, magnesium, flunarizine and amitriptyline, are superior in reducing attack frequency and severity when compared to placebo. The reduction in frequency and severity of migraine attacks for magnesium (64% and 59%, respectively), flunarizine (58% and 63%) and amitriptyline (56% and 49%) and the painfree rates did not reach significance when compared to each other.

Other studies have also confirmed the efficacy of amitriptyline and flunarizine. Amitriptyline was found to be superior to placebo in reducing attack frequency [5–7, 15] and severity [6]. Flunarizine has been compared to placebo and found superior in its effects on attack frequency [9–11, 13] but not on attack severity [9, 10]. This lack of effectiveness of flunarizine on attack severity stands in contrary to our results where the difference was highly significant. Flunarizine has also been shown to have an increased effect in reduction of attack frequency after continuation of treatment after 3 months [10, 11]. This may mean that there could have been a difference between the treatments if they had been continued for longer. But, because of the higher occurrence of side effects like depression reported with longer continuance of flunarizine, we preferred to stop the trial at the end of 3 months [24].

Our high success rates with all medications in our study are an interesting finding, though we do not think that the rates are tremendously high. Pooled data from studies with flunarizine reveal a success rate of 42% [25], while the only placebo-controlled double-blind study with amitriptyline [5] also gave a success rate of 42%. Although our success rates are higher than this we do not think that they are unacceptably high. This seems to be a problem common to many studies involving only a small group of patients (22–24 in our study for all groups) and we think that only cumulative data from many studies or larger studies could reveal the true success rate of a drug. Furthermore our high success rates with magnesium could probably result from the much higher dose of magnesium we used compared to other trials. Future trials comparing our dose with lower doses of magnesium could clarify this. The very high therapeutic gain in our study probably resulted from our low placebo rates rather than high success rates. We are unable to explain the low placebo efficiency (i.e. 12% for attack frequency and 7% for attack severity) in our study. Usually the placebo success rate would be expected to lie between 15% and 25%, percent but interestingly it was much lower in our study. It is possible that the patients noted that placebo was not effective, but there was only one dropout due to ineffectiveness in the placebo group and all remaining patients continued on their drug.

Mg^{+2} has been proposed to play a role in many theories about migraine. Mg^{+2} has a modulatory role on the sensitivity of NMDA receptors to glutamate [26], which plays an important role in the initiation and spreading of cortical depression [27]. Experimental studies have shown that Mg^{+2} can block the spreading cortical depression induced by glutamate and that spreading cortical depression is more easily initiated with low levels of Mg^{+2} in the cerebral cortex [28]. Mg^{+2} also plays an important role in the regulation of the cerebral and peripheral vascular tone [29] by acting like a physiological calcium-channel blocker [16, 30].

Serotonin receptor activity is altered by changes in levels of ionized Mg^{+2} [31, 32] and vasoconstriction induced by serotonin can be effectively blocked by pretreatment with Mg^{+2} [33]. Experimental Mg^{+2} deficiency leads to generation and release of substance P [34] which is thought to act on sensory fibers and cause the pain in headache [35].

Because of these effects, Mg^{+2} has been supposed to play a role in the neuronal and vascular theories for migraine pathogenesis [16] and during the last years many studies have investigated the relation between migraine and Mg^{+2}. Ramadan et al reported lower intracellular Mg^{+2} concentrations in migraine patients versus controls either during or between attacks and suggested that there may be a relation between Mg^{+2} and the triggering of the migraine attack [18]. Later studies have shown that migraine sufferers have low Mg^{+2} levels in the serum and/or saliva [36, 37], erythrocytes [37–40], monocytes and lymphocytes [22, 40, 41]. Mauskop et al. reported that 42% of patients have low ionized Mg^{+2} levels during a migraine attack [17]. It has been proposed that as a result of stress, migraine sufferers excrete Mg^{+2} in increased amounts leading to transient hypomagnesemia in the serum [42]. Besides stress, menstruation, pregnancy, alcohol, many diuretics and reserpine – all known to provoke migraine – are known to produce hypomagnesemia and/or Mg^{+2} wasting [16]. Chocolates and cheeses which provoke migraine contain tryptamine-like substances which in the presence of lowered cerebrovascular Mg^{+2} would result in cerebrovasospasm [16]. A fall in serum ionized Mg^{+2} levels may be the triggering factor in the migraine attack and the following clinical syndrome may be the result of a combination of various pathophysiological mechanisms induced or facilitated by hypomagnesemia. Oral magnesium supplementation might help migraine sufferers to keep a normal serum magnesium concentration, thus preventing low serum magnesium levels from initiating migraine attacks by the mechanisms previously mentioned.

The occurrence of side effects of magnesium in our study was comparable with placebo (47.8% and 41% respectively). One patient in the magnesium group had to discontinue treatment because of severe diarrhea, which ceased after drug withdrawal, one in the flunarizine group because of excessive daytime sedation and 2 patients on amitriptylin had to stop treatment due to remarkable drowsiness. The most common side effect with magnesium was a softened stool in 47.8%. Diarrhea was only seen in 1 patient (4%). This number is somewhat higher than in the studies of Pfaffenrath et al. [20] (28.6%) and of Peikert et al. [21] (18.6%), but in the latter study 2 patients (5%) had to discontinue treatment because of diarrhea [21]. This side effect seems to occur only with oral intake of magnesium, as we did not encounter any gastrointestinal side effects in our study with intravenous $MgSO_4$ [43], nor did Mauskop et al. in a similar study [44]. Our total frequency of side effects with magnesium (47.8%) is comparable to that in other studies which reported frequencies of 37.2% [21] and 45.7% [20]. Our higher rate of side effects might result from the higher doses of magnesium we used.

There were higher frequencies of side effects with flunarizine (72.7%) and amitriptyline (70%) although none of them were serious. Comparison between the side effect frequencies in the treatment groups failed to show any significant difference. Also the dropout rates were not significantly different in the three treatment groups. Although not significant, there seem to be fewer side effects with magnesium. Magnesium, which is also used frequently, parenterally, for the treatment of eclampsia, has not been shown to have adverse effects on the human fetus [45]. Although we have not taken this into consideration in this trial, there is the possibility that magnesium could be used for migraine prophylaxis in pregnancy safely and effectively, where many other current drugs are contraindicated or can only be used cautiously.

Our results with 1830 mg oral magnesium seem to be more effective on attack frequency and intensity and in side effect occurrence when compared to trials using 600 mg oral magnesium. Our dose of magnesium was well tolerated and did not produce more unacceptable side effects and did not lead to a higher dropout rate when compared to trials using lower doses. Dose comparative trials are needed to find the best effective dose for magnesium in the prophylaxis of migraine.

Finally, although this trial was designed as a double-blind study there was no “correct” blinding in regard to the medications given as the 4 different medications were used in different frequencies per day. But it was inevitable to design the study this way as we were comparing 2 drugs which are recommendedly taken at a single dose/day with magnesium which has to be given in multiple doses. As our primary aim was to show whether magnesium was effective or not, we chose to give the placebo group the same frequency of doses as the magnesium group. We still think that there was enough blinding as none of the patients knew what medication they or the other patients were receiving.

This trial shows that magnesium is equally effective and as well tolerated as flunarizine and amitriptyline in migraine prophylaxis. It could be a new treatment option, especially for patients in whom other established drugs are contraindicated, not tolerated or ineffective. As this is the only comparative trial of magnesium in migraine prophylaxis so far and our numbers are small, more and larger comparative trials with magnesium, also comparing first choice drugs like beta-blockers, are needed. The ideal drug for migraine prophylaxis however, a drug that is highly effective in reducing attack frequency but has few side effects, is yet to be found.

References

1. Rasmussen BK (1995) Epidemiology of headache. Cephalalgia 15:45–68
2. Bank J (1994) A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. Headache 34:476–478
3. Tfelt-Hansen P, Standnes B, Kangasneimi P, Hakkarainen H, Olesen J (1984) Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter study. Acta Neurol Scand 69:1–8
4. Verspeelt J, De Locht P, Amery WK (1996) Post-marketing cohort study comparing the safety and efficacy of flunarizine and propranolol in the prophylaxis of migraine. Cephalalgia 16:328–336
5. Gomersall JD, Stuart A (1973) Amitriptyline in migraine prophylaxis. J Neurol Neurosurg Psychiatry 36:684–690
6. Ziegler DK, Hurwitz A, Preskorn S, Hassanein R, Seim J (1993) Propranolol and amitriptyline in prophylaxis of migraine. Arch Neurol 50:825–830
7. Couch JR, Hassanein RS (1979) Amitriptyline in migraine prophylaxis. Arch Neurol 36:695–699
8. Ramadan NM, Schultz LL, Gilkey SJ (1997) Migraine prophylactic drugs: proof of efficacy, utilization and cost. Cephalalgia 17:73–80
9. Sorensen PS, Hansen K, Olesen J (1986) A placebo-controlled, double-blind, cross-over trial of flunarizine in common migraine. Cephalalgia 6:7–14
10. Louis P (1981) A double-blind placebo controlled prophylactic study of flunarizine in migraine. Headache 21:235–239
11. Frenken CWGM (1984) Flunarizine, a new preventive approach to migraine. A double-blind comparison with placebo. Clin Neurol Neurosurg 86:17–20
12. Mendenopoulus G, Manafi T, Logothesis I, Bostantjopoulou S (1985) Flunarizine in the prevention of classic migraine: a placebo-controlled evaluation. Cephalalgia 5:31–37
13. Louis P, Spierings ELH (1982) A comparison of flunarizine and pizotifen in the treatment of migraine. A double-blind study. Cephalalgia 2:197–203
14. Centonze V, Magrone D, Vino M et al (1990) Flunarizine in migraine prophylaxis: efficacy and tolerability of 5 mg and 10 mg dose levels. Cephalalgia 10:17–24
15. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Prekorn SH, Mason J (1987) Migraine prophylaxis: a comparison of propranolol and amitriptyline. Arch Neurol 44:486–489
16. Altura BM (1985) Calcium antagonist properties of magnesium: Implications for antimigraine actions. Magnesium 4:169–175
17. Mauskop A, Altura BT, Cracco RQ, Altura BM (1993) Deficiency in serum ionized magnesium but not total magnesium in patients with migraines. Possible role of ICa^{+2}/IMg^{+2} ratio. Headache 33:135–138
18. Ramadan NM, Halvorson H, Vande-Linde A et al (1989) Low brain magnesium in migraine. Headache 29:590–593
19. Taubert K (1994) Magnesium bei Migräne. Fortschr Med 112:328–330
20. Pfaffenrath V, Wessely P, Meyer C, Isler HR, Evers S, Grotemeyer KH, Taneri Z, Soyka D, Göbel H, Fischer M (1996) Magnesium in the prophylaxis of migraine – a double-blind, placebo-controlled study. Cephalalgia 16:436–440
21. Peikert A, Wilimzig C, Köhne-Volland (1996) Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. Cephalalgia 16:257–263
22. Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G (1991) Magnesium prophylaxis of menstrual migraine: Effects on intracellular magnesium. Headache 31:298–301
23. Headache Classification Commitee of the International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8[Suppl 7]:1–96
24. Sorensen PS, Larsen BH, Rasmussen MJK et al (1991) Flunarizine versus metoprolol in migraine prophylaxis: a double-blind, randomized parallel group study of efficacy and tolerability. Headache 31:650–657
25. Toda N, Tfelt-Hansen P (1993) Calcium antagonists. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches. Raven, New York, pp 383–391
26. Marrannes R, Willems R, Prins E, Wauquıer A (1988) Evidence for a role of the N-methyl-D-aspartate (NMDA) receptor in cortical spreading depression in the rat. Brain Res 457:226–240
27. Ferrari MD (1992) Biochemistry of migraine. Path Biol 40:287–289
28. Mody I, Lambert JDL, Heineman V (1987) Low extracellular magnesium induces epileptiform activity and spreading depression in rat hippocampal slices. J Neurophysiol 57:869–888
29. Altura BM, Altura BT (1978) Magnesium and vascular tone and reactivity. Blood Vessels 15:5–16
30. Iseri LT, French JH (1984) Magnesium: nature's physiologic calcium blocker. Am Heart J 108:188–193
31. Norman AB, Battaglia G, Creese I (1985) [3H]WB4101 labels the 5-HTIA serotonin receptor subtype in rat brain. Mol Pharmacol 28:278–294
32. Turlapaty PD, Altura BM (1980) Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death iscemic heart disease. Science 208:198–200
33. Goldstein S, Zsoter TT (1978) The effect of magnesium on the response of smooth muscle to 5-hydroxytryptamine. Br J Pharmacol 62:507–514
34. Weglicki WB, Phillips TM (1992) Pathobiology of magnesium deficiency: a cytokine/neurogenic inflammation hypothesis. Am J Physiol 263:R734–R737
35. Moskowitz MA (1984) The neurobiology of vascular head pain. Ann Neurol 16:157–168
36. Gallai V, Sarchielli P, Coata G et al (1992) Serum and salivary magnesium levels in migraine. Result in a group juvenile patients. Headache 32:132–135
37. Soriani S, Arnaldi C, De Carlo L et al (1995) Serum and red blood cell magnesium levels in juvenile migraine patients. Headache 35:14–16
38. Schoenen J, Sianord-Gainko J, Lenaert M (1991) Blood magnesium levels in migraine. Cephalalgia 11:97–99

39. Gallai V, Sarchielli P, Morucci P, Abbritti G (1993) Red blood cell magnesium levels in migraine patients. Cephalalgia 13:74–81
40. Mazzotta G, Sarchielli P, Alberti A, Gallai V (1999) Intracellular Mg++ concentration and electromyographical ischemic test in juvenile headache. Cephalalgia 19:802–809
41. Gallai V, Sarchielli P, Morucci P, Abbritti G (1994) Magnesium content of mononuclear blood cells in migraine patients. Headache 34:160–165
42. Durlach J (1976) Neurological manifestations of magnesium imbalance. Handbook Clin Neurol 28:545–579
43. Demirkaya S, Vural O, Ozdag F et al (1999) Efficiency of intravenous magnesium sulphate treatment in acute migraine attacks. Presentation [P03.054] at the AAN 51st Annual Meeting, Toronto, Ontario, Canada (abstract)
44. Mauskop A, Altura BT, Cracco RQ, Altura BM (1996) Intravenous magnesium sulfate rapidly alleviates headaches of various types. Headache 36:154–160
45. Neilson JP (1995) Magnesium sulphate: the drug of choice in eclampsia. BMJ 16(7007):702–703